Long-term Outcomes of Laparoscopic Resection of Gastric Gastrointestinal Stromal Tumors

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Objective: Gastric gastrointestinal stromal tumors (GISTs) are rare neoplasms that require excision for cure. Although the feasibility of minimally invasive resection of gastric GIST has been established, the long-term safety and efficacy of these techniques are unclear. We hypothesized that complete resection of gastric GISTs using a combination of laparoscopic or laparoendoscopic techniques results in low perioperative morbidity and an effective long-term control of the disease.

Methods: Between August 1996 and June 2005, 50 consecutive patients undergoing laparoscopic or laparoendoscopic resection of gastric GISTs were identified in a prospectively collected database. Outcome measures included patient demographics and outcomes, operative findings, morbidity, and histopathologic characteristics of the tumor. Patient and tumor characteristics were analyzed to identify risk factors for tumor recurrence.

Results: Fifty patients, mean age 60 years (range, 34–84 years), underwent 47 local and 3 segmental laparoscopic gastric resections. GI bleeding and dyspepsia were the most common symptoms. Mean tumor size was 4.4 cm (range, 1.0–8.5 cm) with the majority of the lesions located in the proximal stomach. Mean operative time was 135 minutes (range, 49–295 minutes), the mean blood loss was 85 mL (range, 10–450 mL), and the mean length of hospitalization was 3.8 days (range 1–10 days). There were no major perioperative complications or mortalities. All lesions had negative resection margins (range, 2–45 mm). Nine patients had 10 or more mitotic figures per 50 high power fields, while 11 had ulceration and/or necrosis of the lesion. At a mean follow-up of 36 months, 46 (92%) patients were disease free, 1 patient was alive with disease, 1 patient with metastases died of a cardiac event, and 2 (4%) patients died of metastatic disease. No local or port site recurrences have been identified. Patient age, tumor size, mitotic index, tumor ulceration, and necrosis were statistically associated with tumor recurrence. The presence of 10 or more mitotic figures per 50 high power fields was an independent predictor of disease progression ($P = 0.006$).

Conclusion: A laparoscopic approach to surgical resection of gastric GIST is associated with low morbidity and short hospitalization. As found in historical series of open operative resection, the tumor mitotic index predicts local recurrence. The long-term disease-free survival of 92% in our study establishes laparoscopic resection as safe and effective in treating gastric GISTs. Given these findings as well as the advantages afforded by minimally invasive surgery, a laparoscopic approach may be the preferred resection technique in most patients with small- and medium-sized gastric GISTs.

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Gastrointestinal stromal tumors (GISTs) represent a rare but distinct histopathologic group of intestinal neoplasms of mesenchymal origin.[1] Historically, most of these tumors were classified as leiomyomas, leiomyoblastomas, and leiomyosarcomas due to the mistaken belief that they were of smooth muscle origin.[1–3] However, with the advent of electron microscopy and immunohistochemistry, a pleuropotential intestinal pacemaker cell, the interstitial cell of Cajal, was identified as the origin of GISTs.[4] These cells have myogenic and neurogenic architecture and are found within the myenteric plexus, submucosa, and muscularis propria of the gastrointestinal (GI) tract.[4,5] The recent discovery and identification of the CD117 antigen, a c-kit proto-oncogene product, and CD34, a human progenitor cell antigen, in the majority of GIST have led to further delineation of the cellular characteristics of these neoplasms.[6–8]

Although GIST tumors are found throughout the GI tract, the stomach is the site of occurrence in more than half of patients.[2,3,9–11] The most common symptoms of gastric GISTs are GI bleeding and abdominal pain. However, most patients are asymptomatic and the lesions are discovered incidentally during an upper endoscopy performed for other reasons.[12] Their metastatic potential is difficult to predict due to the lack of clear clinical or pathologic signs of malignancy other than obvious metastasis at surgery. In addition, local recurrence or distant metastasis may not present until years after the initial diagnosis.[9] Surgical resection is required for cure of gastric GISTs. In the past, a 1- to 2-cm margin was thought to be necessary for an adequate resection.[12,13] Recently, DeMatteo et al demonstrated that tumor size and not negative microscopic surgical margins determined survival.[2] These findings support the local resection of GIST lesions, including both wedge and submucosal resections. Although the feasibility of minimally invasive resections of gastric GISTs has been established,[11,12,14–18] it has been proposed

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that this approach be limited to lesions <2 cm.[10,19] As a result, the long-term safety of the laparoscopic approach to gastric GISTs, especially for lesions >2 cm, is unclear. We hypothesized that complete resection of gastric GISTs using a combination of laparoscopic or laparoendoscopic techniques results in low perioperative morbidity and effective long-term control of the disease.

MATERIALS AND METHODS

Between August 1996 and June 2005, 50 consecutive patients undergoing laparoscopic or laparoendoscopic resection of gastric GISTs were identified in a prospectively collected database. Patient demographics, clinical presentation, and imaging were analyzed. Perioperative parameters measured included operative times, estimated blood loss, intraoperative findings, surgical techniques, morbidity, and length of hospitalization. In addition, tumor histopathologic characteristics, including size, location, presence of necrosis, and ulceration, tumor marker status, and mitotic activity, were reviewed. Patient and tumor characteristics were analyzed to identify risk factors for tumor recurrence. All operations were performed in a tertiary care hospital by experienced laparoscopic surgeons. Data are expressed as mean ± SD unless otherwise specified. Univariate analysis of factors associated with disease progression (recurrence during the follow-up period) was performed using Wilcoxon rank sum (for ordinal variables) and Fisher exact test (for categorical variables). The subgroup analysis based on mitotic index was performed using Fisher exact test and ANOVA with Tukey's test (if needed). $P \leq 0.05$ was considered significant.

Operative Techniques

The operative approach depended on tumor size, location, and growth morphology. Laparoscopic, laparoendoscopic (intragastric), or laparoscopic hand-assisted wedge or segmental resections were used to treat all gastric lesions in this series. The operating room and trocar set up was similar to that of most of foregut surgeries (Fig. 1). The patient was placed in a supine position with arms abducted on arm boards. A split leg table or stirrups were used in nearly all circumstances, allowing the surgeon to stand between the patient's legs and to directly face the epigastrum. Video monitors were placed lateral to the patient's shoulders. The abdominal cavity was usually accessed in the midline, about one third of the distance between the umbilicus and the xiphoid. After insertion of the initial ports, the patient was placed in a reverse Trendelenburg's position. Prior to the resection, a formal abdominal exploration was performed to rule out peritoneal seeding or hepatic metastasis. An intraoperative ultrasound was used to evaluate the liver for metastases and to guide intraoperative liver biopsy of suspicious lesions. Intraoperative flexible endoscopy was performed in all cases to facilitate localization of the lesion, determine the most appropriate technique for resection, and assist in the evaluation of both the extent of resection margins and the integrity of the staple/suture lines. Importantly, the lesions were never directly manipulated with laparoscopic instruments to avoid the risk of tumor rupture.

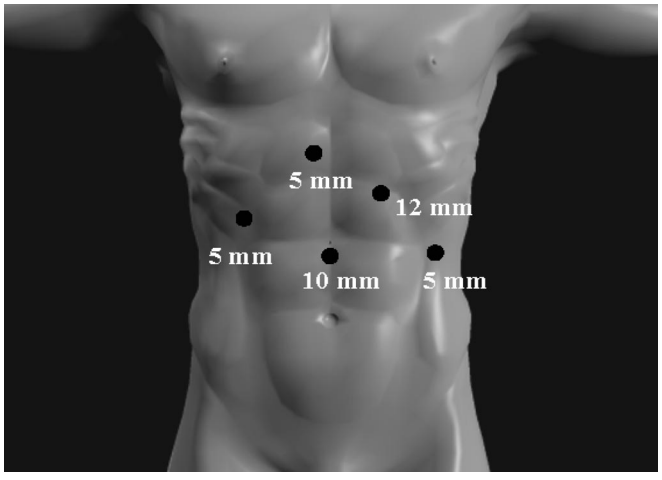

FIGURE 1. Trocar strategy for laparoscopic gastric wedge resections.

Anterior Gastric Wall Tumors

Masses within the anterior wall of the stomach were usually amenable to wedge resection with a linear endoscopic GI anastomosis stapler. After identifying the lesion, the short gastric vessels were divided as needed with ultrasonic coagulating shears. Laparoscopic gastric wedge resection was accomplished by elevating the gastric wall with 2 seromuscular sutures placed opposite each other 1 to 2 cm beyond the mass. The lesion and a cuff of the normal stomach were resected by an endoscopic linear stapler placed just under the sutures. Larger lesions were resected with a margin of normal stomach using ultrasonic coagulating shears. The gastrotomy was closed with a running suture or with an endoscopic linear stapler.

Posterior Gastric Wall Lesions

Posterior wall lesions were commonly approached through the lesser sac. Following the division of the gastrocolic omentum and short gastric vessels, the greater curvature was elevated and rotated cephalad to expose the posterior surface of the stomach. The lesion was then resected similar to the technique described for anterior lesions. One alternative approach to the posterior gastric wall tumors entailed the creation of an anterior gastrotomy over the endoscopically localized lesion. The tumor was then resected with a linear stapler after the lesion was elevated through the gastrotomy with sutures placed in the posterior gastric wall near the tumor.

Intraluminal posterior wall lesions, which were not amenable to the above treatment, especially those at the gastroesophageal junction, were approached via a percutaneous, laparoscopic, intragastric resection. Laparoendoscopic intragastric or "endoluminal" surgery was performed via 2-flange or balloon-tipped laparoscopic trocars (2 or 5 mm) placed percutaneously into the stomach under laparoscopic and endoscopic guidance. A flexible upper endoscope was used for visualization within the stomach during the operation. A dilute epinephrine solution (1:100,000) was injected

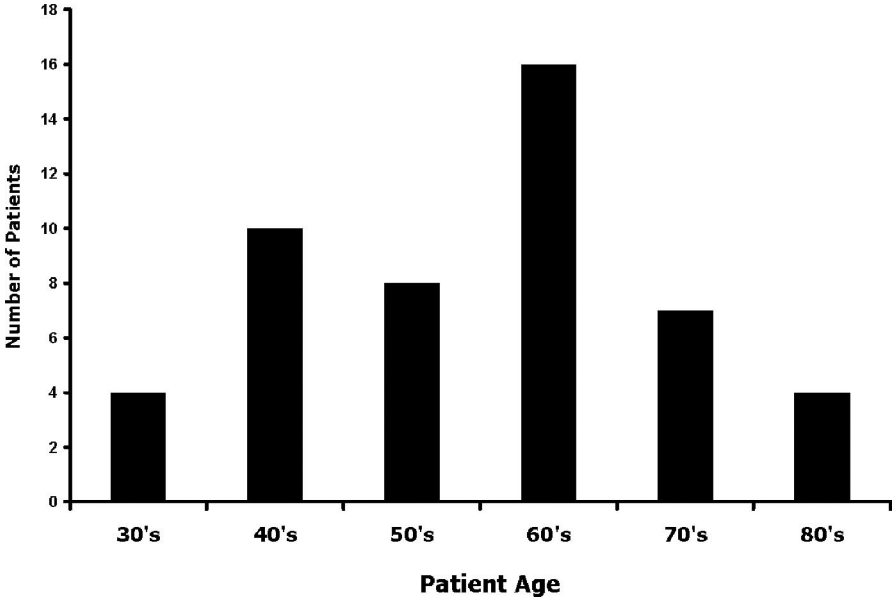

FIGURE 2. Age distribution.

circumferentially around the stromal tumor as a tumescent to aid in dissection of the submucosal plane and to limit bleeding. The lesion was enucleated from the submucosal-muscular junction using an electrocautery hook. The mucosal defect was usually closed with intragastric 2-0 absorbable sutures.

Greater and Lesser Curvature Lesions

Lesions of the greater and lesser curvatures were typically amenable to simple wedge resection with an endoscopic linear stapler. The greater omentum, lesser omentum, or gastrohepatic ligament were divided as needed with the ultrasonic coagulating shears.

Postoperative Care and Follow-up

Postoperatively, nasogastric tubes were routinely used. A gastrograffin swallow was performed in the morning of the first postoperative day in the majority of patients. Diets were subsequently liberalized. Patients were discharged home after tolerating a regular diet. In addition to routine visits at approximately 10 and 30 days after surgery, postoperative follow-up included physical examination every 3 to 4 months for the first 2 years, every 6 months for 2 years, and then yearly. A chest radiograph, abdominal computed tomography (CT) scan, and serum chemistries were obtained at 6 months, 1 year, and then annually for 5 years in a majority of patients with lesions of 3 cm or larger or with mitotic figures. Upper endoscopy was performed at approximately 6 months and 1 year postoperatively and than repeated annually for 2 years. A PET scan, MR imaging, and/or chest CT scan were obtained if abnormalities were found on any of the surveillance studies. All patients were evaluated by an Oncology faculty member for eligibility in a clinical trial or for adjuvant therapy.

RESULTS

Patient Characteristics

From August 1996 to June 2005, 50 consecutive patients undergoing laparoscopic resection of gastric GIST were reviewed. There were 25 men and 25 women. The average age was 60 $\pm$ 13 years (range, 34–84 years). The distribution of patients' ages in our series is summarized in Figure 2. The primary presenting symptoms are summarized in Table 1. However, we believe that most of our patients' symptoms, other than blood loss, were not truly related to the tumor. Five patients who were being followed by their gastroenterologist with repeat endoscopy were referred after their lesion had increased in size. In addition, 4 (8%) patients had lesions discovered during other intra-abdominal surgery or intraoperative endoscopy. All patients (except 1 of the 4 with an incidentally discovered tumor at surgery) underwent preoperative esophagogastroduodenoscopy. In addition, 40 (80%) patients underwent an abdominal CT scan and 10 (20%) patients had an endoscopic ultrasound.

TABLE 1. Main Presenting Signs and Symptoms in the Patients

Presenting Symptom/Sign	No. of Patients
Dyspepsia	16
GI bleed	14
Anemia	10
Abdominal pain	8
Early satiety	4
Dysphagia	4
Asymptomatic	8

The complaints may have been unrelated to subsequently discovered gastric GISTs.

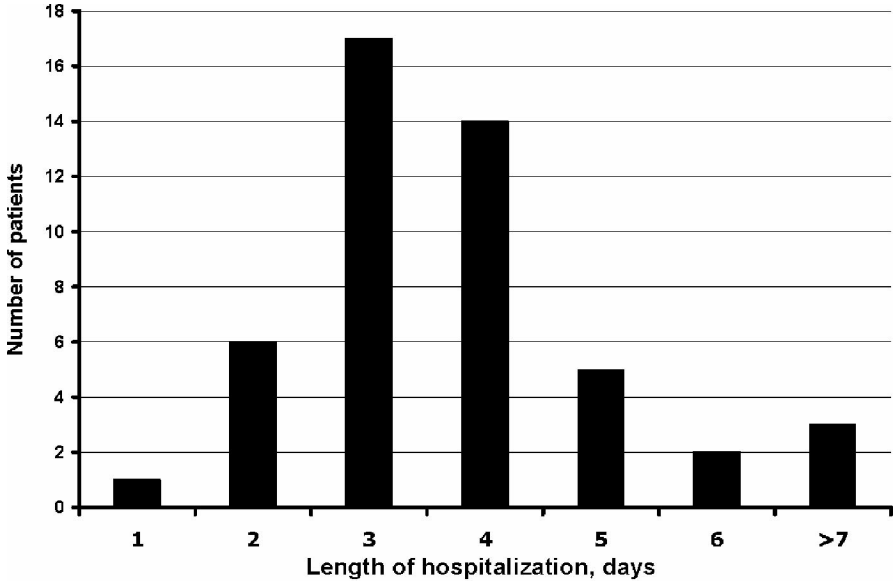

FIGURE 3. Duration of hospital stay.

Perioperative Outcomes

The operative approaches used were: laparoscopic esophagogastrectomy (n = 1), laparoscopic antrectomy (n = 2), laparoscopic stapled wedge gastrectomy (n = 27), laparoscopic transgastric wedge resection (n = 13), laparoendoscopic/endoluminal submucosal resection (n = 4), and laparoscopic hand-assisted wedge gastrectomy (n = 3). In addition, 5 patients underwent 6 concurrent operations: laparoscopic paraesophageal hernia repair in 2, laparoscopic Nissen fundoplication in 2, laparoscopic cholecystectomy in 1, and incisional hernia repair in 1 patient. The average operative time (including additional procedures) was 135 ± 56 minutes (range, 49–295 minutes). The mean estimated blood loss was 85 mL (range, 10–450 mL). There were no episodes of tumor rupture or spillage, no major intraoperative complications, and no conversions to open surgery. Postoperatively, 10 (20%) of patients required nasogastric tubes beyond the 24-hour period. No patient had any evidence of staple-line or anastomotic leak. Postoperatively, 4 patients had minor complications (a trocar site cellulitis, a mild pneumonia, and 2 urinary tract infections). The average length of hospitalization was 3.8 ± 1.6 days (range, 1–10 days) (Fig. 3). There were no major postoperative complications or mortalities. There were no long-term wound related complications and no long-term morbidity related to gastric resection.

Tumor Gross and Microscopic Characteristics

The majority (78%) of tumors were found in the proximal two thirds of the stomach. The exact location of the tumors is summarized in Table 2. The average tumor size was 4.4 ± 2.0 cm (range, 1.0–8.5 cm). All lesions had a negative resection margin of 13 ± 9 mm (range, 1–45 mm). Mucosal ulceration was noted in 11 (22%) of the lesions. Tumor necrosis was found in 12 (24%) lesions. The mitotic index ranged from 0 to 50 mitotic figures (average, 5) per 50 high power fields (HPF). Immunohistochemical analysis included CD117, CD34, S-100, and desmin. CD117 positivity was detected in 39 (78%), and CD34 was positive in 40 (80%) patients. In contrast, S-100 and desmin positivity was rare, occurring in 12 (24%) and 11 (22%) patients, respectively.

TABLE 2. Distribution of Gastric Lesions

Tumor Location	No. (%) of Patients
Proximal stomach	
GE junction	8 (16)
Cardia	9 (18)
Gastric body	
Anterior wall	10 (20)
Posterior wall	4 (8)
Greater curve	6 (12)
Lesser curve	3 (6)
Distal stomach	
Antrum	4 (8)
Prepyloric	6 (12)

A total of 78% were found in the proximal two thirds of the stomach.

Tumor-Related Outcomes

Follow-up information was available for all 50 patients. At a mean follow-up of 36 months (range, 4–84 months), 46 (92%) patients are alive and disease free. Recurrence was noted in 4 (8%) patients. All of those patients had disease recurrence in the liver, with 1 patient having a diffuse intraperitoneal recurrent disease. There were no local recurrences. Two (4%) patients died of metastatic disease. One patient with recurrent disease died of a cardiac event. Another patient with a hepatic recurrence 4 years after the initial resection underwent liver resection and is alive and undergoing adjuvant (imatinib) therapy.

Risk Assessment

Patient characteristics (age and sex), tumor gross (size, location, and resection margin), and microscopic (mitotic

index, cellular markers, presence of necrosis or ulceration) features were analyzed as prognostic factors of disease progression (Table 3). We considered both recurrence and metastasis during the follow-up period as evidence of disease progression. Univariate analysis showed that there was a statistically significant association of disease progression with tumor size ($P = 0.02$), high mitotic index ($P = 0.003$), tumor ulceration ($P = 0.0001$), and tumor necrosis ($P = 0.0001$). Patient sex, tumor location, resection margin, and positive immunohistochemical markers were not associated with adverse prognosis. The presence of >10 mitotic figures per 50 HPF was an independent predictor of disease progression ($P = 0.006$). For further prognostic stratification, the tumors were divided into 3 groups (0–4 mitoses, 5–9, and >10 mitoses per HPF) (Table 4). Group I had 36 (72%) patients, group II had 4 (8%) patients, and group III had 10 (20%) patients. Four of 10 (40%) patients in group III had disease recurrence ($P = 0.001$).

TABLE 3. Assessment of Patient and Tumor Characteristics Predictive of Poor Prognosis (Disease Recurrence)

Patient/Tumor Characteristics	No Recurrence (n = 46)	Recurrence (n = 4)	P
Age (yr)	61	60	NS
Tumor size (cm)	4.2	7.0	0.02
MI	3.4	22.5	0.003
CD117+ [n (%)]	35 (77%)	4 (100%)	NS
CD34+ [n (%)]	36 (78%)	4 (100%)	NS
Ulceration [n (%)]	7 (16%)	4 (100%)	0.0001
Necrosis [n (%)]	7 (16%)	4 (100%)	0.0001

NS indicates not significant; MI, mitotic index (number of mitosis per 50 high power fields).

TABLE 4. Analysis of Patient and Tumor Characteristics Associated With Lesions With Various Mitotic Activity

Patient/Tumor Characteristics	Group I (MI < 5)	Group II (MI 5–9)	Group III (MI ≥ 10)	P
No. of patients	36	4	10	
Mean age (yr)	57	61	68	0.05
Tumor size (cm)	3.9	4.9	6.2	0.003
CD117+ [n (%)]	27 (72)	2 (50)	10 (100)	0.072
CD34+ [n (%)]	28 (78)	3 (75)	9 (90)	0.10
Ulcerations [n (%)]	6 (17)	0	5 (50)	0.072
Necrosis [n (%)]	4 (11)	1 (25)	7 (70)	0.005
Disease progression* [n (%)]	0	0	4 (40)	0.001

MI indicates mitotic index (mitosis per 50 high power fields). Patient age, tumor size, and presence of necrosis are statistically more likely to be associated with lesions with 10 or more mitotic figures per 50 HPF. In addition, lesions with ≥10 mitotic index were significantly more likely associate with disease progression.

*Recurrent or metastatic lesions post resection.

DISCUSSION

Gastric GISTs are rare submucosal lesions that are becoming increasingly encountered because of the rising incidence of upper endoscopy. The identification of the precise cellular origin of these tumors has improved our knowledge of their natural history and malignant potential. Although surgery is the only means for curative therapy for these lesions, the preferred operative approach and extent of resection are still not well established. This manuscript summarizes the outcomes of minimally invasive resection of gastric GISTs in the largest prospective series of patients to date. Our data demonstrate that the laparoscopic or laparoendoscopic approach to local or segmental resections of gastric GISTs results in effective control of the disease with minimal perioperative morbidity and no mortality.

The stomach is by far the most common site of GISTs, occurring in 52% to 60% of cases, with the proximal stomach involved in about two thirds of those patients.[14,20,21] Several studies described that most patients with gastric GIST present in their 6th or 7th decade, with only 10% of patients under 40 years of age.[9,20] We encountered a comparable number (8%) of patients younger than 40 years in this series, but the ages of our patients, in general, were quite mixed (Fig. 3). Although in a univariate analysis patient age was not a significant prognostic factor, we found that older patients were more likely to present with tumors with higher numbers of mitoses.

Most patients in our series were either asymptomatic or had lesions discovered incidentally during a workup of vague dyspeptic or reflux symptoms. Otherwise, anemia or frank GI bleeding from an ulcerated tumor was encountered in 48% of patients. In addition, 4 patients had lesions discovered as a secondary finding during unrelated abdominal surgery. Following upper endoscopy, an abdominal CT scan is usually the test of choice to further delineate the location and size of the lesion and to look for direct or metastatic spread. Endoscopic ultrasound can be very helpful to resolve diagnostic challenges.[14,22] A demarcated hypoechoic mass that is contiguous with the muscularis propria layer of the stomach is characteristic of a GIST.[3,14] While endoscopic biopsies are frequently performed, they uncommonly yield anything more than normal mucosa.[3,14] An endoscopic ultrasound directed needle biopsy, on the other hand, frequently reveals spindle cells or can be positive for specific markers. In addition, a heterogeneous lesion larger than 4 cm and with irregular borders is reported to be highly suspicious for a malignant GIST.[23] However, if the images or pathology of the lesion being investigated do not show clear evidence of benign cyst or mass, it should be resected as a presumed GIST. The minimal morbidity we have experienced with the laparoscopic approach has allowed us to be more aggressive with the management of yet to be diagnosed masses even in patients with a marginal performance status.

Mazur and Clark coined the term "gastrointestinal stromal tumor" in 1983 to describe a distinct group of intestinal sarcomas.[24] More recently, C-kit tyrosine kinase (CD117) has been shown to be expressed by 91% to 99% of the GISTs.[1,9,10,20] This discovery not only substantiated the cellular origin of these tumors but also allowed for a more accurate diagnostic marker. Confounding studies have shown cell differentiation markers to either represent significant predictors of poor prognosis or to be noncontributory.[20,25] Focal desmin expression correlated with a favorable clinical course in Miettinen's series, as none of their patients with a

desmin-positive tumor died of their disease.[9] The positivity or negativity for immunohistochemical markers in our patients was not predictive of tumors' malignant behavior. However, all patients with recurrent or metastatic disease had tumors positive for both CD117 and CD34 and negative for S-100 and desmin. However, the small number of recurrent/metastatic cases in our series precluded us from demonstrating a statistical significance of immunohistochemical markers in predicting tumor biology.

Other histologic features of significance are the presence of necrosis or ulceration.[3,26] Coagulation necrosis has been shown to be associated with malignant behavior.[9] However, it may also be seen in benign tumors, probably representing an infarction or a hemorrhage from the biopsy site. Tumor ulceration is commonly seen in both benign and malignant lesions but their presence confers a statistically higher risk of disease recurrence.[9] We noted the presence of necrosis or ulceration in 24% and 22% of our patients, respectively. Similarly to Meiettinen et al, we identified both features as significant predictors of malignant behavior.

Surgical resection of localized gastric GISTs is the preferred treatment modality.[1,3,10] as resection of the tumor renders the only chance for cure at this time.[2,10] Historically, a 1- to 2-cm margin was thought to be necessary for an adequate resection.[12,13] However, more recently, DeMatteo et al[2] demonstrated that tumor size and not negative microscopic surgical margins determines survival. It is therefore accepted that the surgical goal should be a complete resection with gross negative margins only[2,10] without routine lymphadenectomy.[2] Given this, wedge resection has been advocated by many investigators for the majority of gastric GISTs.[2,10,11,27,28] In some cases, however, tumor size and location may dictate a more extensive surgery, including partial or total gastrectomy,[19,20] as occurred in a few patients in our experience. Because simple resection is appropriate, increasing surgeon experience with laparoscopic gastric surgery (fundoplication, gastric bypass, etc.), the reliability of laparoscopic staplers, and that these tumors can be easily reached with intraoperative endoscopy, the laparoscopic approach to gastric GISTs resection appears very appealing. However, techniques used must avoid direct tumor manipulation with laparoscopic instruments in an effort to eliminate the incidence of tumor rupture. Tumor spillage can results in catastrophic consequences with disease progression, recurrence, and poor survival.[29] In our series, no patient had operative lacerations or rupture of the tumor.

Although the National Comprehensive Cancer Network Clinical Practice Guidelines for Optimal Management of Patients with GIST suggests that laparoscopic techniques should be limited to tumors less than 2 cm,[19] many investigators have reported successful and safe removal of larger GISTs.[12,16,18] Recommendations regarding size criteria amenable to laparoscopic techniques do not appear to be evidence-based. Indeed, it is likely representative of a bias against the use of minimally invasive technology in the oncologic setting or a prescription for caution that was previously seen in several other malignancies. With recent trials confirming safety of laparoscopic techniques in colon, hepatobiliary, and renal oncologic surgeries,[30–32] the role of laparoscopic surgery in resection of GISTs of the stomach should be clarified. We have previously presented a series of laparoscopic versus open resections of 35 gastric GISTs with a mean size of 4.5 cm and some as large as 8 cm.[12] The data demonstrated a reduction in blood loss and hospital stay in the laparoscopic group.[12] Our current series demonstrates the oncologic safety of the laparoscopic approach, with efficacy and recurrence rates similar or superior to historical open surgical controls. The resections were accomplished with minimal morbidity, no perioperative mortality, and short in-hospital convalescence. In addition, we avoided any wound-related morbidity associated with upper abdominal laparotomies. While our series establishes the safety of the laparoscopic techniques in the setting of gastric GISTs, experience in laparoscopic foregut surgery and maintenance of proper oncologic principles are paramount to avoiding intraoperative tumor spillage, incomplete resections, and a subsequent shortened disease-free survival. In addition, the availability of an experienced endoscopist is crucial for intraoperative tumor localization and visualization of the tumor during intragastric resections. We also advocate a hand-assisted technique when needed. Indeed, in 3 patients with large (7.5–8.5 cm) tumors in difficult locations, we used hand-assisted laparoscopy to facilitate tumor manipulation and resection. This technique allows for gentle tumor handling, tactile feedback, and precise placement of endoscopic staplers. The hand-access incision of 6 to 7 cm was also used for safe and easy removal of the large lesions.

Long-term follow up is essential for all patients with GISTs independent of a benign or malignant designation since these tumors have an uncertain biologic behavior. While an active postoperative surveillance program is important, there is no consensus on a standard protocol for following patients. Our approach is to perform a physical examination every 3 to 4 months for 2 years, lengthening the interval to 6 months for approximately 2 years, and then yearly. Chest x-ray (posteroanterior and lateral), abdominal CT scan, and blood tests are obtained yearly. Flexible upper endoscopy is performed as part of the follow-up usually at 6 months and 1 year postoperatively and then annually for the 2 years. PET scanning of the abdomen, MR imaging, and/or chest CT scans are obtained if abnormalities are found on any of the surveillance studies. We focus more heavily on follow-up during the first 2 years due to the fact that most recurrences present during this time period.[3]

Defining meaningful prognostic characteristics of surgically treated gastric GISTs has historically been very elusive. This may have stemmed from inconsistent pathologic diagnosis prior to recognition of C-kit as well as grouping of GISTs from various areas of the GI tract.[10] Several recent studies have provided a comprehensive clinical and histopathologic analysis of gastric GISTs. The emerging consensus favors risk stratification of the tumors over absolute distinction of "benign" versus "malignant."[9,10] Based on a large retrospective analysis, Meiettinen et al classified the tumors as benign, very low, low, low-to-moderate, and high malignant potential.[9] Similar to other previous reports,[20,33,34]

they used tumor size and mitotic activity as the most powerful prognosticators. They demonstrated that even patients with large (>10 cm) gastric GISTs and with low (<5 per 50 HPF) mitotic index have 12% to 15% tumor-related mortality, often after a prolonged (5–15 years) survival. In contrast, even relatively smaller (<5 cm) lesions in the presence of a high mitotic index result in tumor-related deaths in more then than 50% of patients.[9] Another multivariate analysis of 140 surgically resected gastric GISTs found that male sex, tumor size >10 cm, and a mitotic index of 10 or more were significant predictors of poor prognosis.[20] We have also found that tumor size and high mitotic index were statistically associated with a malignant behavior of the lesions in our series. The presence of 10 or more mitotic figures per 50 HPF was a significant predictor of recurrence. In contrast to other investigators, we did not identify patient sex or age as prognostic features of gastric GIST behavior.

Several recent reports have also detailed survival rates of patients with confirmed gastric GISTs. Miettinen et al found a 17% tumor-related mortality at a long-term (up to 20 years) follow up.[9] When patient outcomes were stratified according to lesions' neoplastic characteristics, tumor-related mortality in low-risk lesions was only 2% to 3%. In patients with lesions exhibiting high (>5/50 HPF) mitotic activity, tumor-related mortality was 16% for smaller tumors and up to 86% for lesions larger than 10 cm.[9] Fujimoto et al demonstrated that the 5-year survival in patients with localized disease in series of up to 93%.[20] Similarly, we have experienced a 96% 3-year survival and 92% disease-free survival in our series. However, patient selection bias may have contributed to the high success rate in our series. The patients presenting to our group may have been "preselected" for a laparoscopic resection by the referring physician. It is possible that patients with larger and more advanced gastric GISTs were not sent to us, although 15 patients did have tumors 6 cm or greater in size. Even though we performed 2 open esophagogastrectomies for large (12 and 14 cm) gastroesophageal junction GISTs during the period of this study, we do not view tumor size as a contraindication to a laparoscopic approach, as we have successfully approached laparoscopically lesions as large as 8.5 cm. The applicability of the laparoscopic approach, we believe, should be based on a variety of factors, including patient characteristics, tumor size, invasion, and location, as well as a surgeon's experience and laparoscopic expertise.

CONCLUSION

Gastric GISTs are unusual histopathologic entities in which recurrence remains difficult to predict. Complete surgical resection with negative margins remains the only true means of cure. A minimally invasive approach to gastric GISTs was previously advocated for lesions up to 2 cm only.[19] This series demonstrates that laparoscopic and laparoendoscopic resection of gastric GISTs of sizes up to 8.5 cm is associated with low morbidity and short hospital stays. The tumor mitotic index, size, mucosal ulceration, and necrosis forecast disease recurrence. The long-term disease-free survival of 92% in our study establishes laparoscopic local and segmental resection as safe and effective in treating gastric GISTs. Given this degree of efficacy and the advantages afforded by minimally invasive surgery, a laparoscopic approach may be the preferred resection technique in most patients with small- and medium-sized gastric GISTs.

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Discussions

DR. L. MICHAEL BRUNT (ST. LOUIS, MISSOURI): This series of 50 GIST tumors managed in a minimally invasive fashion is the largest such group reported to date. The authors are to be commended for keeping a prospective database in these patients and for their careful and extended follow-up. They have reported overall excellent outcomes: no conversions, no major complications, and good tumor-related results.

I have a number of questions for Dr. Heniford. The first relate to some of the technical aspects.

I believe the port configuration that you showed is primarily for patients with proximal tumors, which represents the majority of these GISTs, but do you modify your port place if the tumor is located in the distal stomach, and do all of your patients have intraoperative endoscopy?

You mentioned that you also inflated the stomach with the endoscope at the end to test the staple line. Did you identify any leaks by that technique that allowed you then to reinforce the closure?

You had 4 patients who had tumors that were discovered intraoperatively. Were these primarily patients undergoing hiatal hernia repair? If so, how did you approach these? Were any of these around the fundus that you had to resect, and did that compromise your ability to perform a wrap?

In the manuscript you mention obtaining a gastrograffin swallow routinely on postoperative day 1 in all patients. I am wondering if that is still your practice and how useful this was in your study. Did it alter your management in terms of feeding patients at all?

In terms of follow-up, you have a frequent and very thorough follow-up program for these patients with regular CT, endoscopy, and labs. Is it necessary to image patients routinely who are at low risk for developing a recurrent GIST since all your recurrences were in patients with a high mitotic rate and a large tumor size?

The average tumor size in your series was 4.4 cm. I want to know what your indications are now for an open approach or contraindications to a laparoscopic approach other than direct tumor invasiveness. Are you recommending that patients with tumors greater than 5 cm in size are appropriate to approach in this manner?

Finally, I was wondering if could you give us a little more information about the patients who had recurrent disease, what was the nature of the recurrences, their operative procedures, and whether you had any patients that when you resected these tumors laparoscopically you had a positive margin either gross or microscopic. If so, how did you handle that?

DR. B. TODD HENIFORD (CHARLOTTE, NORTH CAROLINA): In answer to your technical question about modifying our technique or our port placement for distal gastric lesions, we do so. We essentially will use the same configuration, but we will just lower the trocars a bit. The camera port, instead of being approximately one third between the umbilicus and the xiphoid, will be at the umbilicus. We did use an EGD in each case except one when an incidental GIST tumor was discovered, and we used an endoscopic ultrasound instead.

As far as leaks go, we had no leaks upon checking the staple line or the suture line in the operating room. To that point, you asked if we do gastrograffin swallows in all of our patients postoperatively. We used to. Only recently we have stopped getting gastrograffin swallows in all of these patients. I have certainly charged a lot of money for negative swallows for patients in these series.

In the 4 patients with intraoperatively discovered GIST tumors, we spoke with the family prior to resecting. In 2 cases, the tumors involved the fundus of the stomach during an antireflux operation. In those cases, we resected them with a laparoscopic stapler, we then oversewed the staple line with a running suture and proceeded similarly to a Collis procedure.

As far as imaging and follow-up in these patients, we are not sure who is going to recur. We have 3 years of follow-up. A majority of patients will recur in the first 2 years, so we are very aggressive in the first 2 years. We tell all our patients that we are not sure who is going to recur and it is difficult for to us know. We usually continue to follow our patients for at least 5 years.

Limitations for open surgery. There were 2 patients not included in this series that we did resect open and did not attempt laparoscopically. One was with a 12 cm and the other

with a 14 cm tumor right at the gastroesophageal junction; those patients underwent an esophagogastrectomy.

As far as recurrent disease and if any of our margins were positive, none of our margins was positive microscopically or grossly in this series; therefore, we can't make comment as to whether that played any role in those patients who did recur.

Dr. Reid B. Adams (Charlottesville, Virginia): In this paper, the authors set out to demonstrate the utility of a minimally invasive approach for the treatment of gastric GISTs and to determine the effectiveness of this approach for long-term control of the disease. This report represents the largest experience to date using this approach, and the authors have elegantly demonstrated that this approach is feasible for the resection of these tumors.

Following appropriate oncologic principles, they successfully treated a large variety of tumors with low morbidity, low mortality, minimal blood loss, and a short length of stay. On this count, their data support their hypothesis.

Regarding long-term tumor control, the data are less clear. This is primarily due to the relatively short follow-up of a mean of 3 years for a disease that can recur 10 to 15 years after resection. Additionally, most of the patients in this series were low-risk patients with small tumors and a low mitotic index.

Despite these limitations, I think the authors' conclusions are correct. They completed resections based on the same principles we use to treat these patients with open resections, and there is no reason to assume that the outcome should be different based solely upon the approach, that is, open or laparoscopic.

Secondly, most patients recur within the first 2 years, as Dr. Heniford said, following the resection and the 3-year disease survival was 92% in this series. Our approach to these tumors has been similar and our experience is similar to yours. We also believe this is an optimal approach to these tumors, if feasible for the treatment and resection of these GISTs.

With these thoughts in mind, I have a number of practical questions about your experience.

First of all, does this series include all GISTs treated at your institution during this time frame? If so, this suggests your conversion rate to an open procedure was zero. Is that a correct assumption? Or were converted patients not included in this review?

Secondly, with the increasing discovery of incidental and therefore small tumors, do you have a size or other criterion to recommend resection? Or do you advocate that all of these tumors be resected regardless of size?

Third, this approach raises a number of technical issues, and it would be helpful for you to comment on these.

First of all, how do you deal with larger tumors adjacent to the GE junction? I have tended to resect these by an open approach primarily due to the difficult reconstruction that can ensue following resection. Do you do these laparoscopically? If so, do you have any tips for the reconstruction? Also, in these patients where the LES may be rendered incompetent, do you add a fundoplication to the reconstruction? Secondly, for tumors along the lesser curve, how do you deal with the vagus nerve? We have elevated the nerve prior to resection in a fashion similar to a parietal cell vagotomy for these patients to avoid postoperative pyloric dysfunction. Have you found this necessary or do you use a different approach than this? Fourth, were there any recurrences in the group undergoing enucleation rather than resection? Finally, do you have any experience with Gleevec for unresectable lesions or to facilitate a minimally invasive approach for the marginally resectable lesion?

Dr. B. Todd Heniford (Charlotte, North Carolina): Were all GISTs included in this series and was our recurrence rate essentially zero? Every patient we attempted laparoscopically, we were able to complete laparoscopically. Indeed, our conversion rate was zero. This did not include all GISTs at our institution. Was there some selection bias in the patients who were sent to us perhaps being somewhat smaller and not involving other organs? Indeed, that may have come into play but we have not seen that.

For incidental or small tumors, do I have a size criterion for those that I would recommend resection? In any patient that has a gastric GIST tumor, if they were a good operative candidate, I would recommend resection. As demonstrated in this study and many others, the larger the tumor, the greater chance that it will be malignant and will recur. I think, as most any tumor that we resect as surgeons, the chance to resect them early before they have a chance to metastasize is appropriate. So if I am confronted with a lesion that is 1 cm, we will resect it.

How do we deal with larger tumors adjacent to the GE junction? Indeed, we do much as you described. Those that are very large and near the lower esophageal sphincter, we have used a hand-assisted technique so we can elevate these lesions with a hand and then staple across them and leave the lower esophageal sphincter competent. The others that have involved the lower esophageal sphincter, right at the lower esophageal sphincter, we have used this transgastric approach I described in 4 patients. We did not do any sort of antireflex operation, believing that if the patient developed reflux we would come back to essentially a virgin abdomen and do a formal antireflex operation.

Recurrences in the group undergoing enucleation. We have had no recurrences in the group undergoing enucleation. And those patients have undergone repeat endoscopy essentially yearly up until they are 3 years out from their surgery.

As far as preoperative Gleevec, we have not used preoperative Gleevec to downstage a tumor to allow to us resect it laparoscopically.

DR. WILLIAM C. WOOD (ATLANTA, GEORGIA): These tumors are little surprise packages. Biology rules. And until-tumors are little surprise packages. Biology rules. And until we have had an Appleman-type analysis by the pathologist where over 50 high powered fields are counted for mitosis, we really don't know whether we have resected something that is probably innocent or something that is malignant. It looked to me on your one slide that you had enucleations with a 1-mm margin. Would you really prospectively settle for an enucleation in something that you thought might well have a high mitotic index?

DR. B. TODD HENIFORD (CHARLOTTE, NORTH CAROLINA): I think that is an extremely difficult question to answer. The first operation I performed at my present institution was in a young woman who helped to run the cancer center. She was scheduled for an Ivor-Levis[1] resection and we performed this type of enucleation at her gastroesophageal junction. She is currently 7 years out and in good health.

We have been very lucky, and there is only one of those tumors that had only one mitotic figure present in 50 high powered fields. So I have not been forced to answer that question to date. I think that it would depend on the patient. I would explain the situation to the patient that survival according to the one study from Sloan-Kettering was not predicted by a microscopically positive margin, and allow that patient to decide if they wanted to undergo a gastroesophageal resection.